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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
JONES, DWAYNE C

ART UNIT	PAPER NUMBER
1614	7

DATE MAILED: 03/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Application No.	Applicant(s)	
	09/921,479	MASON, R. PRESTON	
	Examin r	Art Unit	
	Dwayne C Jones	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *the response of 21 JAN 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-84* is/are pending in the application.

4a) Of the above claim(s) *39-84* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *39-84* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Claims

1. Claims 1-84 are pending.

2. Claims 1-38 are elected and rejected.

3. Claims 39-84 are non-elected and withdrawn from consideration.

Election/Restrictions

4. Applicant's election with traverse of Group I, corresponding to claims 1-38, in Paper No. 6 is acknowledged. The traversal is on the ground(s) that the inventions should be examined together. This is not found persuasive because the restriction requirement of November 1, 2002 clearly pointed out that each of the five (V) groups of claims represents independent and distinct inventions.

5. The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1, 2, 4, 6-12, 14, 16-21, 23, 25-31, 33 and 35-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the compounds of amlodipine, amlodipine besylate, atorvastatin and the hemicalcium salt of atorvastatin, does not reasonably provide enablement for other types of derivatives of

amlodipine and atorvastatin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The instant invention is directed to a pharmaceutical composition of amlodipine and atorvastatin. The method comprises administering amlodipine and atorvastatin.

(2) The state of the prior art

The compounds of the inventions are amlodipine and atorvastatin. The prior art, Buch of U.S. Patent No. teaches of various types of pharmaceutically acceptable salts for the compounds of amlodipine and atorvastatin, (see columns 13-15). However, the

prior art does not teach one skilled in the art of other pharmaceutically acceptable derivatives other than those listed in columns 13-15 of Buch.

(3) The relative skill of those in the art

The relative skill of those in the art of pharmaceuticals is high.

(4) The predictability or unpredictability of the art

The unpredictability of the pharmaceutical art is very high. In fact, the courts have made a distinction between mechanical elements function the same in different circumstances, yielding predictable results, chemical and biological compounds often react unpredictably under different circumstances. Nationwide Chem. Corp. v. Wright, 458 F. Supp. 828, 839, 192 USPQ 95, 105(M.D. Fla. 1976); Aff'd 584 F.2d 714, 200 USPQ 257 (5th Cir. 1978); In re Fischer, 427 F.2d 833, 839, 166 USPQ 10, 24 (CCPA 1970). Thus, the physiological activity of a chemical or biological compound is considered to be an unpredictable art. For example, in Ex Parte Sudilovsky, the Court held that Appellant's invention directed to a method for preventing or treating a disease known as tardive dyskinesia using an angiotensin converting enzyme inhibitor involved unpredictable art because it concerned the pharmaceutical activity of the compound. 21 USPQ2d 1702, 1704-5 (BDAI 1991); In re Fisher, 427 F.2d 1557, 1562, 29 USPQ, 22 (holding that the physiological activity of compositions of adrenocorticotropic hormones was unpredictable art0; In re Wright, 999 F.2d 1557, 1562, 29 USPQ d, 1570, 1513-14 (Fed. Cir. 1993) (holding that the physiological activity of RNA viruses was

unpredictable art); Ex Parte Hitzeman, 9 USPQ2d 1821, 1823 (BDAI 1987); Ex Parte Singh, 17 USPQ2d 1714, 1715, 1716 (BPAI 1990). Likewise, the physiological or pharmaceutical activity of amlodipine and atorvastatin prior to filing of the instant invention was an unpredictable art, especially with derivatives, such as peptides.

(5) The breadth of the claims

The instant claims are very broad. For instance, claims 1, 2, 4, 6-12, 14, 16-21, 23, 25-31, 33 and 35-38 are directed to the plethora of derivatives of compounds {list generic or functional group of compounds}. The breadth of claims was a factor in Amgen v. Chugai Pharm. Co., 927 F.2d 1200, 18 USPQ2d (Fed. Cir.),cert. Denied, 502 U.S. 856 (1991). In the Amgen case, the patent claims were directed to DNA sequences that encoded amino acid sequences. Because a very small change in the amino acid sequence of a protein can result in a very large change in the structure-function activity of a protein and because the laws of protein folding are in such a primitive state, predicting protein structure (and hence, activity) while knowing only the sequence of the protein is akin to predicting the weather for a date in the future. (The length of the claimed peptide ranges from 7 amino acid residues to 68 amino acid residues in length. For claim 1, only 2 residues of the maximum 68 residues are disclosed. The limiting claims that limit the length of the peptide claim still claim peptides only disclose up to four amino acid resides.)

(6) The amount of direction or guidance presented

The amount of guidance or direction needed to enable the invention is inversely related to the degree of predictability in the art. In re Fisher, 839, 166 USPQ 24. Thus, although a single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements, in cases involving unpredictable factors, such as most chemical reactions and physiological activity, more teaching or guidance is required. In re Fischer, 427 F.2d 839, 166 USPQ 24; Ex Parte Hitzeman, 9 USPQ 2d 1823. For example, the Federal Circuit determined that, given the unpredictability of the physiological activity of RNA viruses, a specification requires more than a general description and a single embodiment to provide an enabling disclosure for a method of protecting an organism against RNA viruses. In re Wright, 999 F.2d 1562-63, 27 USPQ2d 1575. In the instant case, given the unpredictability of the physiological or pharmaceutical activity of amlodipine and atorvastatin to be effective in treating arterial and related heart diseases is insufficient for enablement. The specification provides no guidance, in the way of enablement for amlodipine and atorvastatin other than amlodipine besylate and hemicalcium salt of atorvastatin. The specification provides no guidance, in the way written description for derivatives other than amlodipine besylate and hemicalcium salt of atorvastatin. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also In re Wright, 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work. In re Dreshfield, 110 F.2d 235, 45 USPQ 36 (CCPA 1940), gives this

general rule: "It is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result." The article "Broader than the Disclosure in Chemical Cases," 31 J.P.O.S. 5, by Samuel S. Levin covers this subject in detail. A disclosure should contain representative examples, which provide reasonable assurance to one skilled in the art that the compounds fall within the scope of a claim will possess the alleged activity. See In re Riat et al. (CCPA 1964) 327 F2d 685, 140 USPQ 471; In re Barr et al. (CCPA 1971) 444 F 2d 349, 151 USPQ 724.

(7) The presence or absence of working examples

As stated above, the specification discloses of derivatives of the compounds of amlodipine and atorvastatin. However, the instant specification only has enablement for amlodipine besylate and hemicalcium salt of atorvastatin.

(8) The quantity of experimentation necessary

The quantity of experimentation needed to be performed by one skilled in the art is yet another factor involved in the determining whether "undue experimentation" is required to make and use the instant invention. "'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to

the direction in which the experimentation should proceed.'" In re Wands, 858 F.2d 737, 8 USPQ2d 1404 (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 218 (CCPA 1976)). For these reasons, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to determine all of the derivatives of amlodipine and atorvastatin that would be enabled in this specification.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

9. The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

10. Claims 1-8 and 20-27 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Buch of U.S. Patent No. 6,455,574. Buch disclose of pharmaceutical compositions that contain atorvastatin or its pharmaceutically acceptable salt, namely the hemicalcium salt of atorvastatin, and amlodipine along with its pharmaceutically

acceptable salts, such as amlodipine besylate, (see abstract, column 5, lines 30-32, column 7, lines 49-52). In addition, Buch teach of utilizing these pharmaceuticals for treating angina pectoris, atherosclerosis, combined hypertension and hyperlipidemia as well as patients with symptoms of cardiac risk, (see column 1, lines 4-23).

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

12. Claims 1-8 and 20-27 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Chang et al. of U.S. Patent No. 6,262,092. Chang et al. disclose of pharmaceutical compositions that contain atorvastatin or its pharmaceutically acceptable salt, namely the hemicalcium salt of atorvastatin, and amlodipine along with its pharmaceutically acceptable salts, such as amlodipine besylate, (see abstract, claims 19 and 17). Moreover, Chang teach of utilizing these pharmaceuticals for treating hypertension and hyperlipidemia, atherosclerosis, as well as patients with symptoms of cardiac risk, (see claims 9, 13 and 15).

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

15. Claims 1-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Buch of U.S. Patent No. 6,455,574. Buch disclose of pharmaceutical compositions that contain atorvastatin or its pharmaceutically acceptable salt, namely the hemicalcium salt of atorvastatin, and amlodipine along with its pharmaceutically acceptable salts, such as amlodipine besylate, (see abstract, column 5, lines 30-32, column 7, lines 49-52). In addition, Buch teach of utilizing these pharmaceuticals for treating angina pectoris, atherosclerosis, combined hypertension and hyperlipidemia as well as patients with symptoms of cardiac risk, (see column 1, lines 4-23). Although Buch does not specifically teach of inhibiting the crystal formation of cholesterol, it is well known in the art that HMG-CoA reductase inhibitors, in particular atorvastatin, are effective inhibiting HMG-CoA reductase from catalyzing the rate-limiting step of cholesterol biosynthesis. Additionally, Buch is silent to increase in nitric oxide production by endothelial cells with the administration of the very same claimed compounds. However, in both of these instances, applicant is incorporating a functional recitation of a biochemical process.

Accordingly, the skilled artisan would have been most certainly motivated to utilize the teachings of Buch to treat the very same ailments that are claimed by the instant invention. Moreover, it is well within the purview of the skilled artisan to utilize the prior art composition, as taught by Buch, in pharmaceutical preparations, which would inherently perform the functional recitations of inherent biochemical processes that occur with the administration of this previously taught compositions of atorvastatin, and amlodipine.

16. Claims 1-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chang et al. of U.S. Patent No. 6,262,092. Chang et al. disclose of pharmaceutical compositions that contain atorvastatin or its pharmaceutically acceptable salt, namely the hemicalcium salt of atorvastatin, and amlodipine along with its pharmaceutically acceptable salts, such as amlodipine besylate, (see abstract, claims 19 and 17). Moreover, Chang teach of utilizing these pharmaceuticals for treating hypertension and hyperlipidemia, atherosclerosis, as well as patients with symptoms of cardiac risk, (see claims 9, 13 and 15). Despite the fact that Chang et al. do not specifically teach of inhibiting the crystal formation of cholesterol, it is well known in the art that HMG-CoA reductase inhibitors, in particular atorvastatin, are effective inhibiting HMG-CoA reductase from catalyzing the rate-limiting step of cholesterol biosynthesis. Additionally, Chang et al. are silent to increase in nitric oxide production by endothelial cells with the administration of the very same claimed compounds. However, in both of these cases, the applicant is attempting to incorporate a functional recitation of an inherent biochemical process. Accordingly, the skilled artisan would have been most certainly

motivated to utilize the teachings of Chang et al. in order to treat the very same ailments that are claimed by the instant invention. Furthermore, it is well within the level of skill of the artisan to employ the prior art composition, as disclosed by Chang et al., in pharmaceutical preparations that would inherently perform the instantly claimed functional recitations because these biochemical processes that occur with the administration of this previously taught compositions of atorvastatin, and amlodipine, are inherent. Hence, the reference renders the instant invention obvious.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. C. Jones whose telephone number is (703) 308-4634. The examiner can normally be reached on Mondays through Fridays from 8:30 am to 6:00 pm. The examiner can also be reached on alternate Mondays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel can be reached on (703) 308-4725. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

DWAYNE C. JONES
PRIMARY EXAMINER

Tech. Ctr. 1614
March 19, 2003